Peer Review
Experimental Toxicology Division
N H E E R L

MODELING

Evaluating Physiologically-based Pharmacokinetic Models for Use in Risk Assessment

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ENVIRONMENTAL ISSUE: Physiologically-based pharmacokinetic (PBPK) models are increasingly being used in evaluation of the effects of chemical exposures on human health. To date, physiologically-based pharmacokinetic (PBPK) models that have been incorporated into dose-response analyses by the U.S. EPA have been subjected to various forms of internal or external peer-review including review of the methylene chloride PBPK model by the National Academy of Sciences and review of the vinyl chloride PBPK model by government scientists not involved in its development. Due to the increased use of PBPK models, it is evident in the biological modeling community that a universal set of criteria should be established for use in evaluating the quality of a model before it is used in a human health risk assessment.

STUDY GOAL: Develop an organized process and criteria that can be used to evaluate the quality of PBPK models. To a substantial degree, the approaches described here have been or can be applied to other kinds of biological modeling as well.

Process for the Evaluation of PBPK Models

1. Assessment of the Model Purpose
2. Assessment of the Biological Characterizations and Model Structure
3. Assessment of the Mathematical Descriptions
4. Assessment of the Computer Implementation
5. Parameter Analysis and Assessment of the Model Fit
6. Assessment of any Specialized Analyses

1. Assessment of Model Purpose

a. Extrapolations
- High-Dose to Low-Dose Extrapolation
- Route-to-Route Extrapolation
- Cross-Exposure Scenario Extrapolation
- Cross-Species Extrapolation

b. Dose Metric Calculations
- Maximum concentration (C_{MAX})
- Area under the concentration curve (AUC)
- Other applicable dose metrics

2. Assessment of Biological Characterizations and Model Structure

a. Tissue Compartments, Physiological Parameters, Biochemical Parameters

b. Toxicologically Relevant Factors
- Mode of action (known, unknown)
- Active metabolites

e. Cross-Chemical Comparisons
- Information about other chemicals to support or detract from the given model structure

f. Relevant Exposure Scenarios
- Animal pharmacokinetic and toxicity studies
- Human pharmacokinetic and/or epidemiology studies
- Human exposure scenarios needed in risk assessment

3. Assessment of Mathematical Descriptions

a. Check model equations
- Units, mass balance, blood flow balance

b. Evaluate whether mathematical descriptions of the biology are reasonable

4. Assessment of Computer Implementation

a. Review model code for proper syntax and mathematical structure
- Approach is language-dependent
- Difficult to access model equations for models written in languages that use graphical interfaces and/or menu parameterizations

b. Independent re-implementation of a model is a labor intensive option for quality assurance of model coding.

5. Parameter Analysis and Model Fit

a. Review Parameter Documentation

b. Perform Sensitivity Analysis
- Identify the key parameters for which uncertainty and variability will be important determinants of the dose metric(s) proposed for use in the model application.

c. Consider the range of uncertainty in known parameters
- Statistical methodologies for characterizing parameter uncertainty and population variability should be used when possible, but methods are still under development.

d. Evaluate Goodness of Fit
- How well does the model approximate experimental data, including data not used in parameter estimation?
- Statistical methodologies would be useful (e.g. Bayesian methods using Markov Chain Monte Carlo) but are still under development

e. Evaluate Dose Metric Predictions

6. Assessment of any Specialized Analyses

a. Monte Carlo methods used to quantify human variability and potential sensitive populations.

b. Pharmacodynamic Effects
- Enzyme inhibition (e.g. Cholinesterase inhibition by organophosphate pesticides)
- Altered hormone levels

CONCLUSIONS, IMPACT, FUTURE DIRECTIONS

- **A process has been described for evaluating PBPK models proposed for use in Agency risk assessments.**
- **This process is currently being used for reviewing modeling proposed for use in dose response analyses.**
- **Research on sensitivity analysis is ongoing to improve the mathematical characterization of the models.**
- **Research on statistical methods, including Baysian analyses, is needed to develop improved methods for characterizing parameter uncertainty and uncertainty in the model outputs (dose metrics) used in risk assessment.**

SENSITIVITY ANALYSIS IN MODEL EVALUATION

How does sensitivity analysis work?

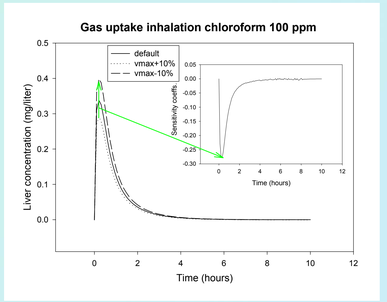
- Start with an experiment designed to estimate a constant using a model.
- Sensitivity coefficients are a measure of change in an experimental variable due to a model parameter.
- If the sensitivity coefficient is zero, then many different values can be used for a constant that will still fit the experimental data. Such an experiment will not provide a unique answer.
- If the sensitivity is greater than zero, then the constant of interest can be determined from the experimental data.

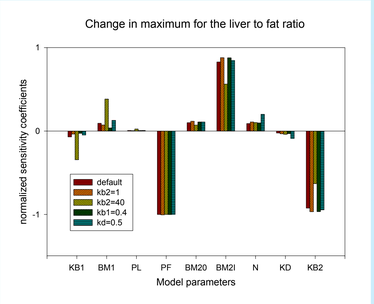
The higher the sensitivity coefficient, the higher the confidence placed in the estimated constant.

- As an example, lets consider closed chamber inhalation experiments designed to estimate metabolic parameters for volatile compounds.
- A bolus of gas is injected into the closed chamber at time zero and allowed to decline to estimate metabolism. Several different concentrations are needed for an individual estimate of metabolic constants.
- Sensitivity analysis was used to illustrate the relationship between the coefficients and the experimental results.

Ranking Importance of model constants

- In order to be able to compare across different models and experimental conditions, sensitivity coefficients are usually normalized.
- The results provide a number generally between zero and one.
- This normalized coefficient is often explained as the percent change in experimental data per percent change in the constant of interest.
- Using normalized coefficients and bar plots, the sensitivity towards different model constants can be ranked for the model output of interest.
- As an example, lets consider a steady-state pharmacokinetic model for dioxin. The liver to fat concentration ratio is dependent on many model constants.
- Normalized sensitivity coefficients allow you to quickly assess which constants are important.





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